## REMARKS

Reconsideration of the above-identified Application is respectfully requested in view of the foregoing amendment and the following remarks. Claims 4,5 and 37-56 remain pending in this case. It is respectfully submitted that all claims contain allowable subject matter and notice of that effect is earnestly solicited.

### I. Rejection under 35 U.S.C. §112 second paragraph

Claims 4 and 5 have been rejected in the Office Action under 35 U.S.C. §112 second paragraph as being indefinite. The Examiner has requested correction on various typos and claim language redundancies.

Claims 4 and 5 have been amended to improve their form and addresses the objections raised by the Examiner in the Office Action.

Amended claims 4 and 5 are now in good order for allowance, and such is earnestly requested.

### II. Rejection under 35 U.S.C. § 103 (A)

Claim 4 stands rejected as being unpatentable under 35 U.S.C. §103(a) over Mulligan et al (U.S. Patent No. 5,674,722) in view of either Mason et al., (U.S. Patent No. 5,643,770) or Takeuchi et al., (1994, *J. Virol.*, 68:8001-8007) and further in view of Herman et al., (U.S. Patent No. 5,792,643).

Claim 5 and claims 37-56 are free of the prior art, and are now in good order for allowance and such is earnestly requested.

#### A. Brief description of the differences between the primary reference of record, Mulligan '722, and the present invention.

Mulligan '722 teaches a replication defective retrovirus (via deletion of *gag*, *pol* and *env* gene encoding sequences) encoding a factor eight (FVIII) B domain deletion (column 26, line 27 to column 27, line 44). The FVIII B domain deletion is prepared using an amphotropic packaging cell line and is capable of infecting human cells (column 27, lines 37-44).

However, Mulligan '722, *does not teach* retrovirus preparations which are resistant to degradation by human complement. Further, Mulligan '722 *does not teach* retrovirus preparations having a titer on human fibrosarcoma cell line HT1080 cells of

greater than $10^6$ cfu/ml. Instead, Mulligan '722 transfects recombinant retroviruses using a mouse-derived cell line, Psi CRIP HIS (clone HIS 19) (Column 27, lines 39-44). The sensitivity or insensitivity of Psi CRIP HIS cells to degradation by human complement systems is simply not disclosed in Mulligan '722.

In contrast, the present invention teaches "preparations of replication defective recombinant retrovirus expressing human factor VIII protein, wherein the recombinant retrovirus is capable of infecting human cells and *is resistant to degradation by human complement*." (Summary of the Invention, page 6, lines 26-28).

The present invention also teaches that "the retroviral vectors of the invention can have a *titer on HT1080 cells of greater than $10^6$*, more preferably $10^7$ cfu/ml and more preferably at least $10^8$ cfu/ml, more preferably $10^9$ cfu/ml, more preferably at least $10^{10}$ cfu/ml, and most preferably $10^{11}$ cfu/ml." (Summary of the Invention, page 7, lines 13-16).

Further the present invention teaches that "within certain embodiments, the titer may be greater than $10^6$ cfu/ml, $10^7$ cfu/ml, $10^8$ cfu/ml, $10^9$ cfu/ml, $10^{10}$ cfu/ml, or $10^{11}$ cfu/ml." (Summary of the Invention, page 7, lines 26-27).

Therefore, although Mulligan '722 teaches preparations for a recombinant FVIII B-domain deletion capable of infecting human cells, Mulligan '722 *does not teach* that the virus after infection is resistant to degradation by the human complement system. Any teachings of a resistance to degradation by the human complement system is taught by the present invention (Example 11, page 139-140), not by Mulligan '722.

Briefly, results in the present invention "demonstrate that recombinant retroviruses which are made in *human packaging cells lines* exhibit no detectable sensitivity to inactivation by heat labile component of human serum, presumably complement, in *in vitro* assays (page 139, lines 7-8 and page 140, line 1)." Whereas, in the same Example (Example 11), cell lines derived from animals including chimps, baboons and macaques show inactivation, or increased sensitivity to degradation, by human complement (page 140, lines 1-3).

In contrast, Mulligan '722 utilize Psi CRIP HIS cells, which are derived from animal, or mice, NIH 3T3 cells. The sensitivity of Psi CRIP HIS cells to degradation by human complement is simply not disclosed in Mulligan '722.

Thus, in the absence of such teachings, a recombinant retrovirus encoding FVIII B domain deletion and packaged using a human cell line HT1080 providing resistance to degradation by human complement is provided for in the present invention, and would not have been obvious to one of ordinary skill in the art based on Mulligan '722.

Moreover, Mulligan '722 retrovirus preparations encoding FVIII B-domain deletion protein do not have a titer on HT1080 cells of greater than $10^6$ cfu/ml. Instead, Mulligan '722 describe the production of high titer stocks in Psi CRIP HIS cells (clone HIS 19) by seeding at $10^5$ to $10^6$ cells in a 10 cm cell culture dish, and achieving approximately 70% confluency after 48 hours (column 28, Example 7, lines 15-20). Thus, Mulligan '722 titers are not performed using HT1080 cells, nor do they result in titers greater than $10^6$ cfu/ml. Greater than $10^6$ cfu/ml titers on HT1080 cells is taught in the present invention.

In the absence of teachings to perform greater than $10^6$ cfu/ml titers on HT1080 cells, Applicants assert that the more efficient HT1080 cell line disclosed in the present invention would not have been obvious to one of ordinary skill in the art based on the Mulligan '722 reference.

**B. The Office Action has not met the burden of establishing a prima facie case of obviousness.**

**1. The Office Action has not met the burden of showing a clear and particular, objective motivation or teaching to combine Mulligan '722 with any other reference or modify Mulligan '722 using knowledge generally available to one of ordinary skill in the art at the time the invention was made.**

In the rejection of claim 4, the Office Action combines Mulligan '722, in view of Mason '770, or Takeuchi et al., and in further view of Herman '643. As the Examiner is aware, and as addressed in previous Responses to Office Actions, the Examiner has the burden of providing evidence of suggestion or motivation to combine these references. The Applicants respectfully assert that the Examiner has not met this burden, and in fact and law, no such burden can be carried based on the cited references in view of the current case law on this issue.

For example, the CAFC recently summarized the law of obviousness as it relates to hindsight and 35 U.S.C. §103 rejections predicated on combined references in *In re Dembiczak* 50 USPQ 2d. 1614 (Dec. 1999) stating:

> "Our case law makes clear that the best defense against the subtle but powerful attraction of hindsight-based obviousness analysis is rigorous application of the ***requirement for a showing of the teachings or motivation to combine prior art references.*** See, e.g. C.R. Bard, Inc. v. M3 Sys., Inc. 157 F,3d 1340, 1352, 48 U.S.P.Q. 2D (BNA) 1225, 1232 (Fed. Cir. 1998) (describing ***"teaching or suggestion or motivation [to combine] as an essential evidentiary component of an obviousness holding"***); *In re Rouffet*, 149 F.3d 1350, 1359, 47 USPQ 2d (BNA) 1453, 1459 (Fed. Cir. 1998) ("the Board must identify specifically...the reasons one of ordinary skill in the art would have been motivated to select the references and combine them"); *In re Fritch*, 972, .2d 1260, 1265, 23 USPQ 2d (BNA) 1780, 1783, (Fed. Cir. 1992) (examiner can satisfy burden of obviousness in light of combination "only by showing some objective teaching [leading to the combination]"); *In re Fine*, 837 2d. 1071, 1075, 5 USPQ 2d (BNA) 1596, 1600 (Fed.)Cir. 1988) (evidence of teaching or suggestion "essential" to avoid hindsight); Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F. 2d 281, 297, 227 USPQ (BNA) 657, 667 (Fed Cir. 1985) (district court's conclusion of obviousness was error when it "did not elucidate any factual teachings, suggestions or incentives from the prior art that showed the propriety of combination")
>
> ...The range of sources available, however, does not diminish the requirement for actual showing. That is, the showing must be clear and particular. ***Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence."*** (emphasis added).

After detailed analysis of the cited references of record, Applicants have been unable to identify any clear and particular, objective evidence or teachings that would motivate a person of ordinary skill in the art to combine the prior art of record. Thus, the

Applicants respectfully assert that the Examiner has not provided any objective evidence of motivation to combine.

Moreover, the teachings of the combined references are provided in the present disclosure, not in parts pieced together from the prior art. More particularly, one cannot use hindsight reconstruction to pick and choose among isolated disclosures to depreciate the claimed invention. *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d (BNA) 1596, 1600 (Fed. Cir. 1988).

Thus, the Examiner needs to provide clear and particular objective evidence of a teaching or motivation to combine the diverse references cited as required by the CAFC, or withdraw her 35 U.S.C. §103 rejections.

**2. There is no reasonable expectation of success when combining Mulligan '722 .**

The Office Action has divided 4 major areas of the present invention: 1) a replication defective virus encoding FVIII, or FVIII B domain deletion; 2) human packaging cells lines including human fibrosarcoma cell line HT1080 capable of infecting human cells; 3) insensitivity, or resistance, to degradation by human complement system; and 4) high titer virus particles on HT1080 cells greater than $10^6$ cfu/ml.

First, the Office Action combines the primary reference of Mulligan '722 with Mason '770 and Herman '643. In this combination of prior art references, Mulligan '722 teaches items 1 and 2 above, but does not teach items 3 and 4. However, Mason '770 teaches item 3 and Herman '643 teaches item 4. Thus, the Office Action has combined the shortcomings of Mulligan '722 by combining Mulligan '722 with the teachings of Mason '770 and Herman '643.

Alternatively, the Office Action combines the primary reference of Mulligan '722 with Takeuchi et al., and Herman '643. Again, Mulligan '722 teaches items 1 and 2 above, but does not teach items 3 and 4. However, Takeuchi et al., teaches item 3 and Herman '643 teaches item 4. Thus, the Office Action has combined the shortcomings of Mulligan '722 by combining Mulligan '722 with the teachings of Takeuchi et al., and Herman '643.

However, Applicants assert that by combining Mulligan '722 with at least two other prior art references, the Office Action has caused undue experimentation on the part of one with ordinary skill in the art.

Previously, the court established in *In re Wands*, that in regards to biotechnology/chemistry cases, specifications/disclosures that do not provide expressly detailed working examples are non-enabling. *In re Wands*, 858 F.2d, 8 USPQ 2d 1400 (Fed. Cir. 1988). Thus, in the absence of specific details and working examples, there is no reasonable expectation of success of achieving the 4 items above based on the invention of Mulligan '722 alone, or in combination with Mason '770 and Herman '643, or alternatively, in combination with Takeuchi et al., and Herman '643 without "undue experimentation."

Also, as stated previously, one cannot use the instructions of the present invention to piece together the teachings of the prior art. That is, hindsight reconstruction to pick and choose among isolated disclosures to depreciate the claimed invention is not proper under 35 U.S.C. §103. *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d (BNA) 1596, 1600 (Fed. Cir. 1988).

**III. Conclusion**

In view of the above remarks, it is submitted that all pending claims (4, 5 and 37-56) are in condition for allowance and allowance is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changed made.**"

No additional fees are seen as being necessary in connection for this amendment. However, the Examiner is authorized to charge any additional fees or credit any overpayment to Deposit Account 16-2230.

If any issues remain, the Examiner is urged to contact the undersigned by telephone for a prompt resolution thereof.

Respectfully submitted,

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**Version With Markings To Show Chang d Made**

4. (Amended) A preparation of replication d fective recombinant retrovirus expressing human factor VIII protein, wherein said recombinant retrovirus is capable of infecting human cells and is resistant to degradation by human complement, wherein said recombinant retrovirus preparation has a [title] titer of HT1080 cells of greater than $10^6$ cfu/ml.

5. (Amended) A preparation of replication defective recombinant retrovirus expressing human factor VIII protein, wherein said recombinant retrovirus is capable of infecting human cells and is resistant to degradation by human complement [wherein said recombinant retrovirus preparation has a title of HT1080 cells of greater than $10^6$ cfu/ml], wherein said retrovirus preparation has a titer of HT1080 cells of grater than $10^7$ cfu/ml.